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labels and other advertisements, are feeding "fake" orange beverages to their children under the impression that they are giving them the orange juice recommended by their physician. Unfortunately, these preparations, as a rule, contain no orange juice and are lacking in the organic acids and the vitamines which give medicinal value to the genuine orange juice. In most instances they are sweetened carbonated water, flavored with a little oil from the peel of the orange and artificially colored to imitate orange juice, say the officials of the Bureau of Chemistry.

That Bureau, charged with the enforcement of the Federal food and drugs act, therefore, has ruled that the terms "ade" "squash," "punch," "crush," and "smash," when used in conjunction with the name of a fruit, can be applied correctly only to beverages which contain the edible portion of the fruit or juice of the fruit named.

It has been observed, the food officials say, that these spurious orange beverages, when sold, are not usually labeled as orange juice, since such labeling would be a direct violation of the food and drugs act. Frequently the labels contain statements, in a more or less inconspicuous place, that the beverage contains no orange juice. The manufacturer, it is held, tries to mislead the purchasers by suggestive statements and pictures played up prominently on the label so as to attract instant attention and convey the impression that the product is really orange juice and, at the same time, he endeavors to escape the charge of misbranding by seeming to correct the misleading features with inconspicuous statements in another part of the label, which the average purchaser does not read.

Prosecutions have been instituted by the Bureau of Chemistry, United States Department of Agriculture, under the Pure Food and Drugs Act, against this form of misbranding, and cases are now in the Federal courts. Pending decision by the courts, the food officials say, some firms are still using what are held to be deceptive labels.

A word of warning by physicians when recommending orange juice will go a long way toward preventing mothers from being misled by these deceptive labels and advertisements. The best way to get orange juice for children is to buy the fruit and squeeze out the juice.

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## THE EFFECT OF SHAKING ALKALINIZED AQUEOUS SOLUTIONS OF ARSPHENAMINE AND AQUEOUS SOLUTIONS OF NEOARSPHENAMINE IN THE PRESENCE OF AIR.

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The exposure of alkalinized aqueous solutions of arsphenamine and aqueous solutions of neoarsphenamine to the air has been shown by Ehrlich to increase markedly the toxicity of both compounds.[1]

[1] Ehrlich, Paul, Soziale Kultur und Volkswohlfahrt, 1913.

For this reason the manufacturers, in their printed directions which accompany these products, state that solutions of either compound must be used as promptly as possible after they are prepared for administration. However, they do not advise against shaking in the presence of air when preparing the solutions for clinical use.

Inasmuch as a certain amount of shaking is always done in making solutions of either compound, it was thought advisable to determine whether shaking certain aqueous solutions in the presence of air might affect the toxicity of these compounds in the same manner as exposure to the air has been shown to influence them.

*Arsphenamine.*—Samples of arsphenamine are frequently obtained, which, upon the addition of normal sodium hydroxide to their aqueous solutions, form rather dense precipitates that redissolve with difficulty in excess of the alkali, and which require considerable shaking to effect their solution promptly.

The effect of shaking a solution of arsphenamine which had been made alkaline with sufficient sodium hydroxide to form the disodium salt, was therefore determined in the following manner: Twenty c. c. of a 2 per cent aqueous solution of disodium arsphenamine[1] was made from a high grade domestic arsphenamine.[2] The solution was then divided into equal parts and each 10 c. c. was transferred to a 25 c. c. glass-stoppered cylinder. One part served as control and the other was shaken vigorously in the cylinder, at room temperature (about 20° C.), either by hand or by means of a shaking machine; the number of excursions in either case was about 250 per minute.

These solutions were then given intravenously to white rats, which were taken from the same stock and which were alike as regards their weight and condition. The rate of injection was the same for the administration of both solutions. In all the experiments except those of set E, the shaken solution was administered first; in set E the rats alternately received shaken and control solutions. The results of the experiments on alkalinized arsphenamine are given collectively in Table I.

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[1] One c. c. of normal sodium hydroxide was used for each 100 mgms. of arsphenamine. This was a trifle more than was necessary to form the disodium salt.

[2] The maximal tolerated dose for the white rat or the dose tolerated by 60 per cent or more of the animals for 48 hours when given intravenously as a 2 per cent alkaline solution, 0.9 c. c. normal sodium hydroxide being used for each 100 mgms. of arsphenamine, was 140 mgms. per kilo. The minimal lethal dose or the dose required to kill 60 per cent or more of the animals in 48 hours when given as above, was 160 mgms. per kilo.

TABLE I.—*The effect on toxicity of shaking a 2 per cent alkalinized aqueous solution of arsphenamine in the presence of about twice its volume of air, as shown by the death rate in white rats after its intravenous administration.*

| Set. | Shaken. Length of time shaken. | Dose, mgm. per kilo. bodyweight. | Number injected. | Number died within 48 hours. | Number lived 48 hours. | Remarks. | Set. | Not shaken (controls). Dose, mgm. per kilo. bodyweight. | Number injected. | Number died within 48 hours. | Number lived 48 hours. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 10 min.. | 100 | 5 | 3 | 2 | Solution dark greenish yellow. Rats all very sick; resisted injection. | A | 100 | 5 | 1 | 4 | Rats only slightly sick, did not resist injection. |
| B | ...do.... | 100 | 5 | 5 | 0 | .....do..... | B | 100 | 5 | 1 | 4 | Do. |
| C | ...do.... | 60 | 5 | 2 | 3 | | C | 60 | 5 | 0 | 5 | |
| D | 1 min... | 100 | 5 | 2 | 3 | | D | 100 | 5 | 1 | 4 | |
| E | ...do.... | 100 | 5 | 5 | 0 | Received the drug alternately with controls. | E | 100 | 5 | [1] 2 | 3 | |
| F | ...do.... | 70 | 5 | ..... | 5 | | F | 70 | 5 | 1 | 4 | |

[1] One pregnant; other, caseous masses in lungs.

It is shown by Table I that shaking alkalinized aqueous solutions of arsphenamine for 10 minutes in the presence of air caused changes not only in the color of the solutions but in their toxicity as well. The original color of these solutions was a light canary-yellow. After the solution was shaken for 10 minutes, its color deepened to a dark greenish-yellow. The toxicity increased at least 60 per cent, as shown by the fact that the shaken solution killed over 60 per cent of the animals within 48 hours at the dosage of 100 mgm. per kilo, while solutions not shaken were previously found to kill a like percentage of the animals in the same period at 160 mgm. per kilo. Shaking for 1 minute caused only a slight deepening in the color of the solution, but a decided increase in its toxicity. These experiments further indicate that the increase in toxicity was due to changes which occurred during the first minute of the shaking, since solutions shaken either for 1 minute or 10 minutes killed over 60 per cent of the animals within 48 hours at the dosage of 100 mgm. per kilo and were tolerated by 60 per cent or over for 48 hours at 60 and 70 mgm. per kilo.

*Neoarsphenamine.*—The various market preparations of neoarsphenamine as a rule are so readily soluble in water at room temperature that shaking is usually unnecessary to assist in dissolving them promptly. Occasionally, however, the powder forms a gelatinous mass upon the addition of water. If this occurs, vigorous shaking may be required to break up the partially dissolved mass.

Under certain conditions some lots of neoarsphenamine, which were readily soluble in water when manufactured, later become

difficultly soluble. Such preparations are usually shaken to hasten their solution. It has been shown by previous studies that such preparations are almost always highly toxic for animals, even when not shaken, and therefore they should not be used clinically.

Experiments to determine the effect of shaking neoarsphenamine solutions were made with two samples of domestic neoarsphenamine, products of two different manufacturers, both samples being readily soluble in water at room temperature. They will be designated as Lots B and P.[1]

In the following tests each sample was made up as follows: Twenty c. c. of a 4 per cent aqueous solution was made up with freshly distilled water at room temperature (about 20° C.). Ten c. c. of the 4 per cent solution was then transferred to a 25 c. c. glass cylinder and shaken vigorously for varying periods, the shaking being done either by hand or by means of a shaking machine. The number of excursions in either case was about 250 per minute. The other 10 c. c. was not shaken and served as a control. These solutions were then given intravenously and at a constant rate to white rats, which were from the same stock and were about the same as regards weight and condition. The shaken solution was given first in all cases. The results with Lot P are shown in Table II; with Lot B in Table III.

TABLE II.—*Effect on toxicity of shaking a 4 per cent aqueous solution of neoarsphenamine (Lot P) in the presence of about twice its volume of air, as shown by the death rate in white rats after its intravenous administration.*

| Shaken. | | | | | | Not shaken (controls). | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Set. | Length of time shaken. | Dose, mgm. per kilo. bodyweight. | Number injected. | Number died within 7 days. | Number lived 7 days. | Remarks. | Set. | Dose, mgm. per kilo. bodyweight. | Number injected. | Number died within 7 days. | Number lived 7 days. | Remarks. |
| H | 10 min.. | 200 | 5 | 5 | 0 | No change in color of solution after shaking. | H | 200 | 5 | 0 | 5 | |
| I | ...do..... | 140 | 5 | 5 | 0 | | I | 140 | 5 | 0 | 5 | |
| J | ...do..... | 100 | 5 | 4 | 1 | | J | 100 | 5 | 0 | 5 | |
| K | ...do..... | 90 | 5 | 1 | 4 | Same solution. | K | 100 | 5 | 0 | 5 | Served as control for both 90 and 70 mgm. doses. |
| K | ...do..... | 70 | 5 | 1 | 4 | | | | | | | |
| L | 5 min... | 200 | 5 | 5 | 0 | | L | 200 | 5 | 0 | 5 | |
| M | 2 min... | 200 | 5 | 2 | 3 | | M | 200 | 5 | 0 | 5 | |
| N | 1 min... | 300 | 5 | 5 | 0 | Rats very sick after injection. | N | 300 | 5 | 0 | 5 | Stood one-half hour. |
| O | ...do..... | 200 | 5 | 2 | 3 | | O | 200 | 5 | 0 | 5 | |
| P | ...do..... | 140 | 5 | 3 | 2 | | P | 140 | 5 | 0 | 5 | |

[1] The maximal tolerated dose for the white rat or the dose tolerated by 60 per cent or more of the animal or seven days when given intravenously as a 4 per cent aqueous solution for P was 420 mgm. per kilos for B, 200 mgm. per kilo. The minimal lethal dose or the dose which kills 60 per cent or more of the animals within seven days when given as above described was found to be 500 mgm. per kilo for P, and 240 mgm. per kilo for B. In all these determinations at least five rats were injected at the same dosage.

TABLE III.—*Effect on toxicity of shaking a 4 per cent aqueous solution of neoarsphenamine (Lot B) in the presence of twice its volume of air, as shown by the death rate in white rats after its intravenous administration.*

| Set. | Shaken. | | | | | Remarks. | Set. | Not shaken (controls). | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Length of time shaken. | Dose, mgm. per kilo. bodyweight. | Number injected. | Number died within 7 days. | Number lived 7 days. | | | Dose, mgm. per kilo. bodyweight. | Number injected. | Number died within 7 days. | Number lived 7 days. |
| Q | 1 min..... | 200 | 5 | 5 | 0 | No change in color of solution after shaking. | Q | 200 | 5 | 1 | 4 |
| R | ...do..... | 100 | 5 | 1 | 4 | | R | 100 | 5 | 0 | 5 |
| S | 30 sec..... | 200 | 5 | 5 | 0 | | S | 200 | 5 | 1 | 4 |
| T | 10 sec..... | 200 | 5 | 1 | 4 | | T | 200 | 5 | 0 | 5 |
| U | 5 sec..... | 200 | 5 | 1 | 4 | | U | 200 | 5 | 0 | 5 |
| V | 10 min.... | 50 | 5 | 0 | 5 | | V | 50 | 5 | 0 | 5 |

Table II (Lot P) shows that shaking a high-grade neoarsphenamine for 10 minutes as above described increases its toxicity over fourfold, whereas shaking for 1 minute converts it into a border-line preparation when tested at the Hygienic Laboratory standard test dose of 200 mgm. per kilo. No change in color occurred in these solutions even after they had been shaken for 10 minutes; therefore change in color is no criterion by which to judge the toxicity of a solution of this lot of neoarsphenamine. In set N the rats which received the shaken solution were all very sick after the injection; however, on the smaller doses no marked effects of a similar kind were observed.

Table III (Lot B) deals with a border-line neoarsphenamine, that is, it was tolerated by rats receiving the Hygienic Laboratory standard test dose of 200 mgm. per kilo, but failed at a 20 per cent higher dosage.

These experiments (Lot B) demonstrate that a relatively low-grade preparation will tolerate a certain amount of shaking and yet pass the Hygienic Laboratory tests, since shaking for 5 and 10 seconds caused only 1 death in 5 in each set. Inasmuch as all the control rats survived, these deaths might indicate that there was a slight increase in the toxicity when the solution was shaken for these short periods. However, if shaken for 1 minute or even 30 seconds, the increase in the killing properties of this lot is strikingly seen. On the other hand, shaking the solution for two minutes will not increase its toxicity fourfold as was the case with Lot P, probably because the initial toxicity of Lot P is lower. In contradistinction to Lot P, solutions of Lot B when shaken for 10 minutes showed a distinct deepening in the color of the solution to a rather deep golden-yellow.

In order to ascertain whether the increase in the toxicity of these solutions was due to oxidation or to some purely physical change in the solution, the following experiment was conducted:

A 10 c. c. glass-stoppered cylinder was filled with a 4 per cent solution of Lot B and before stoppering, 25 glass beads, each having a diameter of 3 mm., were placed in the fluid. The cylinder was then stoppered so that no visible air bubbles were included and shaken vigorously for 1 minute. The shaken solution was then tested against a control solution in the usual way at the dosage of 200 mgm. per kilo, using 10 animals for the set. The shaken solution caused no deaths, whereas the control solution caused one death in the five rats injected.

This experiment indicates that air is essential to the production of an increase in the toxicity of this compound and that the probable change which occurs is the oxidation of the neoarsphenamine to p-oxyphenylarsenoxide, commonly called "arsenoxide," which we know to be many times more toxic than neoarsphenamine.

One may naturally conclude from the foregoing experiments that any procedure other than shaking, which brings the solution in intimate contact with the air, will also likely result in an increase in its toxicity. The practice of making a solution in an open mortar or in a large beaker, as is sometimes done, should therefore be abandoned.

*Summary:* Shaking alkalinized aqueous solutions of arsphenamine or aqueous solutions of neoarsphenamine in the presence of air renders them highly toxic, as shown by intravenous administration to white rats. The increase in toxicity caused by such shaking is presumably due to the oxidation of these compounds to p-oxyphenylarsenoxide, commonly called "arsenoxide," inasmuch as shaking a solution of neoarsphenamine in the absence of air does not increase the toxicity of such a solution.

*Conclusion:* The toxicity of alkalinized aqueous solutions of arsphenamine or aqueous solutions of neoarsphenamine is greatly influenced by the manner in which they are prepared for administration.